Topical or oral antibiotics for children with acute otitis media presenting with ear discharge: study protocol of a randomised controlled non-inferiority trial

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ABSTRACT

Background Around 15%–20% of children with acute otitis media present with ear discharge due to a spontaneous tear or perforation of the eardrum (AOMd). Current guidance recommends clinicians to consider oral antibiotics as first-line treatment in this condition. The opening in the eardrum however should allow topical antibiotics to enter the middle ear directly. Local administration of antibiotics does not expose children to systemic side effects and may put less selective resistance pressure on bacteria. Evidence on the effectiveness of this approach in children with AOMd is lacking.

Methods and analysis A primary care-based, open, individually randomised, controlled, non-inferiority trial. The trial aims to recruit 350 children aged 6 months to 12 years with AOM and ear pain and/or fever. Participants will be randomised to 7 days of hydrocortisone-bacitracin-collisine eardrops five drops three times daily or amoxicillin oral suspension 50 mg/kg body weight per day, divided over three doses. Parents will keep a daily diary of AOM symptoms, adverse events and complications for 2 weeks. In addition, they will record AOM recurrences, healthcare utilisation and societal costs for 3 months. The primary outcome is the proportion of children without ear pain and fever at day 3. Secondary outcomes include ear pain and fever intensity/severity; days with ear discharge; eardrum perforation at 2 weeks; adverse events during first 2 weeks; costs; and cost effectiveness at 2 weeks and 3 months. The primary analyses will be intention-to-treat and per-protocol analyses will be conducted as well.

Ethics and dissemination The medical research ethics committee Utrecht, The Netherlands has given ethical approval (17-400/G-M). Parents/guardians of participants will provide written informed consent. Study results will be submitted for publication in peer-reviewed medical journals and presented at relevant international scientific meetings.

Trial registration number The Netherlands National Trial Register; NTR6723. Date of registration: 27 November 2017.

Strengths and limitations of this study

► The pragmatic, open-label design of our trial enhances the applicability of the findings to daily practice.
► The pragmatic design is most suited to address key secondary outcomes such as antibiotic consumption during the first 2 weeks and cost-effectiveness in everyday practice.
► The open-label design may introduce bias caused by the awareness of treatment assignment.

INTRODUCTION

Acute otitis media (AOM) is one of the most common childhood infections and an important reason for doctor consultations and antibiotic prescribing. Approximately 15%–20% of children with AOM present with ear discharge due to a spontaneous tear or perforation of the eardrum (AOMd). Contrary to widespread beliefs, children with AOMd have similar levels of ear pain and are more unwell at presentation than those without ear discharge. These children also have a poorer prognosis with higher rates of ear pain and/or fever at 3–7 days and more AOM recurrences and hearing problems at 3 months than children presenting with AOM without ear discharge. They also benefit more from oral antibiotics than those with AOM without ear discharge: number needed to treat to achieve resolution of ear pain and/or fever at days 3–7: 3 versus 8, respectively. Based on this evidence, current guidelines recommend general practitioners (GPs) to consider an immediate oral antibiotic prescribing strategy for children with AOMd. Oral antibiotics, however, expose children to systemic side effects such as
diarrhoea, vomiting and rash⁷ and routine use of oral antibiotics in common infections such as AOM contributes to emergence of antimicrobial resistance.⁸⁹ Alternative treatment strategies for AOM are therefore urgently needed.

In children with AOMd, the perforation should allow topical antibiotics to enter the middle ear directly. Topical antibiotic treatment does not expose children to systemic side effects and may put less selective resistance pressure on commensal microbes.¹⁰¹¹ We have shown that in children with acute ear discharge in the presence of ventilation tubes (grommets) antibiotic-corticosteroid eardrops are clinically much more effective and less costly than oral antibiotics.¹²¹³ Topical antibiotics may therefore also be an effective treatment strategy in children with AOMd. So far, evidence to support this hypothesis is lacking.¹⁴¹⁵ Our trial aims to provide this key evidence.

OBJECTIVE

The aim of this randomised controlled trial is to establish whether treatment with antibiotic-corticosteroid eardrops is non-inferior to treatment with oral antibiotics in children aged 6 months to 12 years presenting to their GP with AOM with acute ear discharge due to a spontaneous tear or perforation of the eardrum (AOMd).

The objectives are to determine the:

- Effectiveness of antibiotic-corticosteroid eardrops versus oral antibiotics in terms of:
  - The proportion of children without ear pain and fever at day 3;
  - Severity and duration of ear pain, fever, ear discharge;
  - Time to resolution of total symptoms;
  - Middle ear effusion (MEE) and eardrum perforation at 2 weeks;
  - Otitis media (OM)-specific quality of life (QoL) at 2 weeks and 3 months;
  - Antibiotic consumption during the first 2 weeks and at 3 months and AOM recurrences at 3 months;
  - Adverse events during the first 2 weeks;

- Costs and cost-effectiveness of antibiotic-corticosteroid eardrops versus oral antibiotics;

- Prevalence of bacteria and viruses in otorrhea and nasopharyngeal samples of children with AOMd before and after treatment and the antimicrobial susceptibility profile of the bacteria;

- Impact of the treatment regimens on antimicrobial resistance genes in the human gut.

METHODS AND ANALYSES

Study design and setting

An open, individually randomised, controlled, non-inferiority trial in 350 children aged 6 months to 12 years presenting to their GP with AOMd. Children will be randomly allocated to 7 days treatment with either: (1) antibiotic-corticosteroid (hydrocortisone–bacitracin–colistin) eardrops or (2) oral antibiotics (amoxicillin suspension). Follow-up will be 3 months.

At trial commencement, in December 2017, we anticipated a 2-year trial recruitment period. Approximately 250 GPs in the region of Utrecht, The Netherlands, agreed to recruit children to the trial. Due to the COVID-19 related infection control measures, we anticipate a relatively low AOM incidence during trial recommencement. To meet the required sample size, we will recruit additional general practices to the trial. Further details on the trial status are outlined in the ‘current study status’ section below.

Participants

Children aged 6 months to 12 years presenting to their GP with recent onset AOMd in one or both ears and either ear pain or fever or both. Children with grommets in place and those with a pre-existing perforation of the eardrum are excluded. For detailed inclusion and exclusion criteria, see box 1. AOM presenting with ear discharge due to a spontaneous tear or perforation of the eardrum (AOMd) is defined as the presence of acute-onset of otoscopically confirmed otorrhea together with other symptoms of an acute infection such as ear pain and/or fever, and/or irritability.

Inclusion and baseline assessments

Figure 1 depicts a flow diagram of study procedures. Participating GPs inform parents of potentially eligible children about the trial, take consent for sharing their contact details with the research team at the UMC.
Utrecht and provide a study information letter. Members of the research team contact parents by phone to provide detailed information about the trial. If parents provisionally agree to participate and if the child meets the eligibility criteria, a home visit by the trial doctor is scheduled for the same day.

At this visit, the trial doctor takes written informed consent from parents/guardians, collects baseline demographic and disease-specific data, records otoscopic findings and takes otorrhoea, nasopharynx and faeces samples. Parents will complete an OM-specific QoL questionnaire on behalf of their child.

Study group assignment

An independent data manager generates a computer-generated randomisation sequence with stratification according to age (<2 vs ≥2 years) and laterality (unilateral vs bilateral AOM at baseline). At the conclusion of the baseline home visit, the trial doctor accesses a trial randomisation website for concealed study-group assignment. The assignment will be balanced in a 1:1 ratio for the two study groups:

1. Hydrocortisone–bacitracin–colistin (Bacicoline-B) eardrops, five drops, three times per day in the discharging ear(s) for 7 days; or
2. Amoxicillin, 50 mg/kg of body weight per day, divided over three doses administered orally for 7 days.

Hydrocortisone–bacitracin–colistin eardrops were also used in our previous trial in children with acute ear discharge in the presence of ventilation tubes (grommets). Parents of children assigned to the antibiotic-corticosteroid eardrops group will be shown how to remove any visible ear discharge with a tissue and apply the drops while tilting their child’s head to one side, and to apply tragal pressure (tragal pumping).

Amoxicillin is listed as first-line antibiotic for AOM in children in most European guidelines, including the Netherlands. Based on the current antimicrobial resistance profiles in the Netherlands, the clinical practice guideline refers to the Dutch Paediatric Formulary which recommends a dosage of 50 mg/kg of body weight per day, divided over three doses for 7 days.

The study team will notify the GP and local pharmacist about the result of the randomisation. During follow-up, parents and GPs are encouraged to manage AOM recurrences according to current Dutch clinical practice guideline, but any treatment decisions will be up to the GPs’ discretion. Being a pragmatic trial, no restrictions in concurrent treatment will be applied and any concurrent treatments will be captured in the daily symptom diary.

Follow-up data collection

Participants will be followed for 3 months. Parents will keep a daily diary of AOM-related symptoms including fever recordings and ear pain scores, use of study and other medication, adverse events and complications of AOM for 2 weeks. Thereafter, they will keep a weekly diary recording AOM recurrences, GP consultations, prescribed and over-the-counter (OTC) medication, hospital admissions and societal costs for AOM for 3 months. A telephone call will be scheduled at day 3 to answer any remaining questions about the study, to optimise compliance to the diary and to capture data on our most critical parent-reported outcomes. A follow-up visit at the child’s home will be scheduled at 2 weeks to check
diary data for accuracy, perform otoscopy and tympanometry and sample otorrhoea (where possible), nasopharynx and faeces samples. Parents will complete OM-specific QoL and productivity loss questionnaires at 2 weeks and at 3 months. Parents will also send a faeces sample to the laboratory for analysis at 3 months.

**Validated questionnaires**

Parents report the presence and severity of their child’s symptoms using a validated seven-point Likert scale. OM-specific QoL of the child will be assessed using the parent-reported OM-6 questionnaire, a 6-item questionnaire recording ear-related problems in the previous period. An adapted version of the MTA Productivity Cost Questionnaire (iPCQ) is used to capture parental productivity losses due to AOM.

**Temperature measurement**

Parents measure their child’s temperature two times per day (morning and evening) with a tympanic membrane thermometer in the unaffected ear. In children aged below 2 years and in those with unilateral ear discharge, temperature is measured rectally. To standardise measurements, a study thermometer will be provided. The definition of ‘no fever’ at day 3 (primary outcome) is a temperature recording below 38.0°C both in the morning and evening.

**Eardrum perforation**

Otoscopy will be used to assess the integrity of the eardrum at 2 weeks. In case of inconclusive otoscopy results, tympanometry results will be used.

**MEE assessment**

A diagnostic algorithm combining tympanometry and otoscopy will be used to diagnose MEE at 2 weeks.

**Collection and analyses of otorrhoea and nasopharynx samples**

The otorrhoea and nasopharynx samples are collected using a flexible applicator swab with flocked nylon fibre tip. The swabs will be immediately transported to the microbiology laboratory of the UMC Utrecht where they will be stored at −80°C until further analysis.

**Collection and analyses of faeces samples**

The baseline, 2-week and 3-month faeces samples are collected using the OMNIgene●GUT (OMR-200), a trademark of DNA Genotek, Ottawa, Canada. Parents will send the 3-month faeces samples by mail. If faeces samples cannot be collected during the baseline and 2-week home visit, we will provide the parents with a collection kit and transport envelop, so parents can collect and send the faeces samples by mail at their earliest convenience. Samples will be stored at −80°C at the microbiology laboratory of the UMC Utrecht until analysis for detection and quantification of the dynamics of bacterial genes that confer resistance to the antibiotics used in our trial.

**Primary and secondary outcomes**

The primary outcome is the proportion of children without ear pain (ear pain score 0 on the 0–6 Likert scale) and fever (body temperature of 38.0°C or higher) at day 3 (72 hours after randomisation).

Secondary outcomes are the proportion of children with at most mild ear pain (ear pain score less than 3 on the 0–6 Likert Scale) at day 3; mean ear pain score over days 0–3; number of days with ear pain (ear pain score 1 or higher on the 0–6 Likert scale); mean body temperature over days 0–3; number of days with fever (body temperature of 38.0°C or higher) during the first 2 weeks; the proportion of children with parent-reported ear discharge at day 3; number of days with parent-reported ear discharge at day 3 and during the first 2 weeks; proportion of children with otoscopically confirmed ear discharge at 2 weeks; time to resolution of total symptoms (time to all of pain, fever, discharge, being unwell, sleep disturbance, and distress/crying being rated 0 or 1 on the Likert scale); MEE and proportion of children with otoscopically confirmed eardrum perforation at 2 weeks; OM-specific QoL at baseline, 2 weeks and 3 months; antibiotic consumption during the first 2 weeks and at 3 months; number of AOM recurrences at 3 months; number of adverse events during the first 2 weeks; costs and cost-effectiveness at 2 weeks and 3 months; the prevalence of viruses and bacteria in otorrhoea and nasopharynx samples at baseline and 2 weeks; the antimicrobial susceptibility profiling of the bacteria and the impact of the treatment regimens on antimicrobial resistance genes in the human gut; microbiome profile of nasopharynx at baseline and 2 weeks.

**Sample size calculation**

The main aim is to demonstrate that antibiotic-corticosteroid eardrops are non-inferior to oral antibiotics in relieving ear pain and fever at day 3. The proportion of children without ear pain and fever at day 3 is expected to be 65% in the oral antibiotics group and around 35% if placebo or no treatment would be trialled. Our parent panel assisted in defining the non-inferiority margin by advising on the maximum difference in primary outcome that they would regard as unimportant. Following these discussions, the clinically acceptable non-inferiority margin is set at 15%; that is, 50% of the difference (30%) observed between oral antibiotics and placebo or no treatment in earlier trials. Taking 50% of such a difference is also a widely-accepted method to determine the non-inferiority margin. Testing significance at a one-sided 0.025 level (α) and using a power of 80% (β 0.20), each treatment arm should include at least 150 children to demonstrate that the upper limit of the one-sided 97.5% CI (or equivalently a two-sided 95% CI) of the difference in treatment effect for the primary outcome does not exceed the predefined non-inferiority margin of 15%. To allow for a maximum of 10% loss to follow-up, we aim to randomise 350 children.
STRICTUAL ANALYSIS

Primarily, all analyses will be performed according to the intention-to-treat principle. Per-protocol analyses will also be conducted as well because of its importance in non-inferiority trials. All analyses will be performed blinded with respect to study-group assignment and analysis and presentation of results will be in accordance with the Consolidated Standards of Reporting Trials guidelines.

Clinical effectiveness

We will use descriptive statistics to describe the baseline characteristics trial population; we will present means and SD for normally distributed continuous variables, medians and IQRs for non-normally distributed continuous variables, and numbers with percentages for categorical variables.

The primary outcome will be analysed with binomial logistic regression model including treatment group and effectiveness of oral antibiotics versus antibiotic-corticosteroid eardrops will be expressed as relative risk and absolute risk difference with accompanying 95% CIs. This latter will enable us to judge whether non-inferiority has been demonstrated, in particular whether the upper limit of the two-sided 95% CI exceeds the predefined non-inferiority margin of 15%. In adjusted analyses, stratification factors and other important prognostic factors (baseline ear pain score, duration of ear pain prior to enrolment) will be added to the model. Subgroup effects according to age (<2 vs ≥2 years) and laterality (unilateral vs bilateral AOM at baseline) will be evaluated by including an interaction term (treatment*age) in the model.

In sensitivity analyses, we will impute for missing baseline and outcome data using multiple imputation techniques. In further sensitivity analysis, we will assess whether results differ when defining the absence of fever for the primary outcome as parental fever score 0 or 1 on the 0–6 Likert scale at day 3 (instead of the child’s body temperature recordings as specified above).

In secondary analysis, we will use log binomial regression analyses for dichotomous variables, Poisson regression analyses for count variables, and linear regression analyses for continuous variables, where applicable corrected for repeated measurements. For these analyses, the comparison between treatment groups will be expressed as risk ratios, rate ratios, and mean differences, respectively; all with 95% CIs. Kaplan-Meier curves will be plotted for duration of symptoms and log-rank tests for differences between groups.

Cost-effectiveness analysis

A societal perspective will be used for this analysis, that is, medical and non-medical costs will be taken into account. We will use a short-time horizon for all analyses and therefore, all costs will be presented undiscounted.

First, effectiveness will be assessed: the main clinical effectiveness outcome will be symptom (ear pain and fever) resolution. Similar to previous trials in this field, we will not use quality-adjusted life-years (QALYs) as the nature of the condition (self-limiting in the vast majority of the children and of relatively short duration) does not impact importantly on QALYs.

Second, costs will be calculated; all costs will be estimated at the patient level by multiplying resource use with cost estimates per unit of resources use. Cost prices will be estimated according to guidelines for economic evaluation in healthcare research or taken from standard reference lists, as far as possible. Costs of medication use will be retrieved from the Dutch formulary and a pharmacist’s fee will be added for every prescription. Costs of OTC and complementary medicines will be calculated per day, based on current average retail prices. Costs of consulting a GP or a medical specialist, and hospitalisations will be based on current Dutch guidelines for pharmacoeconomic evaluation or charges if no other estimates are available. Costs of diagnostic tests will also be derived from the Dutch guidelines for pharmacoeconomic evaluation. Costs of surgical procedures will be based on a previous Dutch costing study. Costs associated with absence from work will be retrieved from the completed iPCQ. The hourly cost estimate for childcare will be derived from the Dutch National Institute for Family Finance Information. Travel expenses will be calculated for healthcare visits following the Dutch guideline for pharmacoeconomic evaluation. Overall costs will be compared across the treatment groups, and where relevant, differences will be calculated, including 95% CIs. Finally, we will compare differences in costs between treatment groups to differences in clinical effects between groups by calculating incremental cost-effectiveness ratios (ICERs). ICERs will indicate the incremental cost per day with ear pain and fever avoided when comparing antibiotic-corticosteroid eardrops with oral antibiotics, both in the short (14 days) and long term (3 months). Uncertainty will be addressed in a probabilistic sensitivity analysis by means of bootstrapping. Results will be presented using incremental cost-effectiveness planes and cost-effectiveness acceptability curves.

ETHICS AND DISSEMINATION

The study is conducted according to the principles of the Declaration of Helsinki (10th version, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and the principles of Good Clinical Practice. The medical research ethics committee Utrecht, The Netherlands has approved the protocol (protocol number 17-400/M-G). The trial doctor will take written informed consent (see online supplemental file 1) from both parents/guardians. Regular trial audits including checks on source data verification, accuracy, validity and completeness of informed consent forms and captured data will be performed by a clinical research associate of Julius Clinical, an independent clinical research organisation. We have not established a data safety monitoring
board and refrain from conducting any interim analysis for safety or superiority/futility since we neither expect any safety issues nor large differences in treatment failures between the two active treatment groups given the difference (30%) observed between oral antibiotics and placebo or no treatment in previous trials. However, in accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The data management department of the Julius Center for Health Sciences and Primary Care of the UMC Utrecht will be responsible for handling and storage of the data using innovative software applications like SLIM (Study Logistic and Information Management System) and Research Online. On completion of the trial, data will be stored for a minimum of 15 years at a central data drive at the Julius Center and will only be made available for use by third parties on request and approval of the principle investigator (professor RAMJD).

**Dissemination plan**
We will publish study results in peer reviewed scientific journals and present at relevant (inter)national scientific meetings. We will work with our parent panel to help interpret the findings of the trial and harness their resources for dissemination to the lay public.

**PATIENT AND PUBLIC INVOLVEMENT**
For this trial, we have established a panel of eight parents. This panel provided input to the design of the trial including the sample size calculation by advising on the clinically acceptable non-inferiority margin and the outcome measures by proposing additional outcomes of interest such as being unwell and sleep disturbance, and commented on the recruitment strategy and patient information letter. One of the parent panel members is a coapplicant on the grant application and coauthor on this paper. The parent panel will be actively involved throughout all critical stages of the trial through regular parent panel meetings. They will work with us throughout the recruitment phase, will be involved in reporting the trial results, and will be ultimately key to pull the evidence into mainstream clinical practice.

**CURRENT STUDY STATUS**
The first participant was enrolled in the trial on 13 December 2017. On 8 August 2018 with 34 participants being enrolled, trial recruitment was put on hold due to supply issues of hydrocortisone–bacitracin–colistin eardrops. These drops are available again since early 2021. Our funding body, the Netherlands Organisation for Health Research and Development (ZonMw), has approved the trial to reopen in September 2021. We expect data collection to be completed by the end of 2023 with trial results being available by March 2024.

**DISCUSSION**
This trial is one of the first to compare the effectiveness of topical with oral antibiotics in children with AOMd. The only other trial in this field is conducted in UK primary care (Runny Ear STudy). This study has been designed in close collaboration with members of the Dutch study team to enable future meta-analysis by harmonising design, outcomes and outcome measure instruments. The UK-based trial has stopped prematurely due to problems with the electronic health record system platform which resulted in low recruitment (n=22) and failure to reach the predefined sample size.

With obvious theoretical advantages of topical over oral antibiotic treatment and the lack of direct evidence, further research is needed to establish whether with AOMd can effectively be treated with topical antibiotics. Our trial will not only provide this key evidence, but also establish the impact of the two antibiotic treatment strategies on microbiome composition and antimicrobial resistance. The pragmatic, open-label design of our trial enhances the applicability of the findings to daily practice and is most suited to address key secondary outcomes such as antibiotic consumption during the first 2 weeks and cost-effectiveness in everyday practice. This would be much more difficult to determine realistically in a blinded study where children in both groups would receive oral suspension and ear drops. The lack of blinding might, however, introduce bias caused by the awareness of treatment assignment which may be particularly problematic in trials with subjective outcomes. However, both study groups receive an active treatment, our parent panel had no strong beliefs or preferences for one treatment over the other, and a recent meta-epidemiological study found no evidence for a difference in estimated treatment effect between blinded and non-blinded trials.

Another limitation of our study is, that we do not capture data on the prevalence of longer term complications such as the presence of otoscopically confirmed MEE or chronic supplicative OM at 3 months. We, however, will collect information about AOM-related specialist referrals, hospitalisation and/or surgery during the 3 months follow-up period, which provide information on the occurrence of AOM sequelae in the short and long term.

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REFERENCES
26 Bootsma H, Haakkaart-van Roijen L, Koopmanschap M. Manual of the IMTA productivity cost questionnaire (iPCQ). Rotterdam: IMTA Rotterdam; Erasmus University, 2013. www.imta.nl
40 Farmacotherapeutisch Kompas - CVZ. Available: http://www.fk.cvz.nl/
43 Hay AF, Moore M, Taylor J. Results, lessons learned and recommendations from the REST randomised controlled trial of antibiotic strategies for children with acute otitis media with discharge. 2021 Submitted to Health Technol Assess; provisionally accepted 2021.